CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:NDA 20-774

ADMINISTRATIVE DOCUMENTS

Perio Chip
NDA Number 20-774

PATENT INFORMATION AND CERTIFICATION

Perio Chip
NDA Number 20-774

PATENT INFORMATION AND CERTIFICATION

US Patent No.	Expiration Date	Patent Type	Name/Address Patent Owner	Name of US agent authorized to receive notice of patent certification
5,002,769	March 16, 2006	Compositions for the Sustained-Release of Chlorhexidine	Yissum Research Development Company of the Hebrew University of Jerusalem 46 Jabotinsky Street POB 4279 Jerusalem 91042 Israel	Sterne, Kessler, Goldstein & Fox Attorneys at Law 1100 New York Avenue, N.W. Suite 600 Washington, D.C. 20005-3934
5,023,082	March 30, 2005	Sustained-Release Pharmaceutical Compositions	Yissum Research Development Company of the Hebrew University of Jerusalem 46 Jabotinsky Street POB 4279 Jerusalem, Israel	Sterne, Kessler, Goldstein & Fox Attorneys at Law 1100 New York Avenue, N.W. Suite 600 Washington, D.C. 20005-3934

005

The United States of America

The Commissioner of Patents and Trademarks

Has received an application for a patent for a new and useful invention. The title and description of the invention are enclosed. The requirements of law have been complied with, and it has been determined that a patent on the invention shall be granted under the law.

Therefore, this

United States Patent

Grants to the person or persons having title to this patent the right to exclude others from making, using or selling the invention throughout the United States of America for the term of seventeen years from the date of this patent, subject to the payment of maintenance fees as provided by law.

Harry F. Manbeck, Jr.

Commissioner of Patents and Trademarks

Linda D. Elliott

Attest

(142)

ATTACHMENT #1

REQUEST FOR TRADEMARK REVIEW

To: Labeling and Nomenclature Committee
Attention: Dan Boring, Chair (HFD-530) NLRC

From: Division of DERMATOLOGIC & DENTAL DRUG PRODUCTS		HFD-540
Attention: JIM VIDRA	Phone: 827-2067	
Date: 1-7-97		
Subject: Request for Assessment of a Trademark for a Proposed New Drug Product		
Proposed Trademark: PERIO CHIP™ (PerioChip™)	NDA/[redacted]# 20-774	
Established name, including dosage form: Chlorhexidine gluconate chip		
Other trademarks by the same firm for companion products:		
Indications for Use (may be a summary if proposed statement is lengthy): PerioChip™ is indicated as a part of scaling and root planing procedures for the treatment of periodontitis.		
Initial Comments from the submitter (concerns, observations, etc.): The word "perio" appears in many dental product names. Please review this name to avoid sound-alike names or confusing prefixes.		

Note: Meetings of the Committee are scheduled for the 4th Tuesday of the month. Please submit this form at least one week ahead of the meeting. Responses will be as timely as possible.

Rev. August 95

Consult #742 (HFD-540)

PERIOCHIP chlorhexidine gluconate chip

There were no look-alike/sound-alike conflicts or misleading aspects found in the proposed proprietary name. However, the Committee feels the most appropriate established name for this product is (chlorhexidine gluconate periodontal system) to be in conformance with USP nomenclature conventions.

The Committee has no reason to find the proposed proprietary name unacceptable.

/S/ 3/4/97

CDER Labeling and Nomenclature Committee, Chair

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action.

NDA/BLA # 20-744 Supplement # _____ Circle one: SE1 SE2 SE3 SE4 SE5 SE6

HFD-540 Trade and generic names/dosage form: PERIOCHIP Action: (AP) AE NA

Applicant PERIO PRODUCTS Therapeutic Class 38

Indication(s) previously approved _____

Pediatric information in labeling of approved indication(s) is adequate ___ inadequate ___

Proposed indication in this application REDUCTION OF POCKET DEPTH IN INDIVIDUALS WITH ADULT PERIODONTITIS

FOR SUPPLEMENTS, ANSWER THE FOLLOWING QUESTIONS IN RELATION TO THE PROPOSED INDICATION.

IS THE DRUG NEEDED IN ANY PEDIATRIC AGE GROUPS? ___Yes (Continue with questions) ___No (Sign and return the form)

WHAT PEDIATRIC AGE GROUPS IS THE DRUG NEEDED? (Check all that apply)

__Neonates (Birth-1month) __Infants (1month-2yrs) __Children (2-12yrs) __Adolecents(12-16yrs)

___ 1. **PEDIATRIC LABELING IS ADEQUATE FOR ALL PEDIATRIC AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric age groups. Further information is not required.

___ 2. **PEDIATRIC LABELING IS ADEQUATE FOR CERTAIN AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for certain pediatric age groups (e.g., infants, children, and adolescents but not neonates). Further information is not required.

___ 3. **PEDIATRIC STUDIES ARE NEEDED.** There is potential for use in children, and further information is required to permit adequate labeling for this use.

___ a. A new dosing formulation is needed, and applicant has agreed to provide the appropriate formulation.

___ b. A new dosing formulation is needed, however the sponsor is either not willing to provide it or is in negotiations with FDA.

___ c. The applicant has committed to doing such studies as will be required.

- ___ (1) Studies are ongoing,
- ___ (2) Protocols were submitted and approved.
- ___ (3) Protocols were submitted and are under review.
- ___ (4) If no protocol has been submitted, attach memo describing status of discussions.

___ d. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

X 4. **PEDIATRIC STUDIES ARE NOT NEEDED.** The drug/biologic product has little potential for use in pediatric patients. Attach memo explaining why pediatric studies are not needed. PERIODONTITIS IS A DISEASE OF ADULTS.

Fred Hyman 4/21/98

___ 5. If none of the above apply, attach an explanation, as necessary.

ARE THERE ANY PEDIATRIC PHASE IV COMMITMENTS IN THE ACTION LETTER? ___ Yes X No

ATTACH AN EXPLANATION FOR ANY OF THE FOREGOING ITEMS, AS NECESSARY.

5/14/98

This page was completed based on information from MEDICAL OFFICER (e.g., medical review, medical officer, team leader)

/S/ _____ 4/21/98

Name of Preparer and Title Date

/S/ 5/14/98

cc: Orig NDA/BLA # 20-744
HFD-540/Div File
NDA/BLA Action Package
HFD-006/ KRoberts

(revised 10/20/97)

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

NDA/PLA # 20-774 Supplement # _____ Circle one: SE1 SE2 SE3 SE4 SE5 SE6

HFD-540 Trade (generic) name/dosage form: PERIOCHEP Action: AP (AE) NA

Applicant PERIO PRODUCTS Therapeutic Class 35

Indication(s) previously approved _____

Pediatric labeling of approved indication(s) is adequate ____ inadequate ____

Indication in this application REDUCTION OF POCKET DEPTH IN INDIVIDUALS WITH ADULT PERIODONTITIS

(For supplements, answer the following questions in relation to the proposed indication.)

___ 1. **PEDIATRIC LABELING IS ADEQUATE.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric subgroups. Further information is not required.

___ 2. **PEDIATRIC STUDIES ARE NEEDED.** There is potential for use in children, and further information is required to permit adequate labeling for this use.

___ a. A new dosing formation is needed, and applicant has agreed to provide the appropriate formulation.

___ b. The applicant has committed to doing such studies as will be required.
- ___ (1) Studies are ongoing,
- ___ (2) Protocols were submitted and approved.
- ___ (3) Protocols were submitted and are under review.
- ___ (4) If no protocol has been submitted, explain the status of discussions on the back of this form.

___ c. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

X 3. **PEDIATRIC STUDIES ARE NOT NEEDED.** The drug/biologic product has little potential for use in children. Explain, on the back of this form, why pediatric studies are not needed.

___ 4. **EXPLAIN.** If none of the above apply, explain, as necessary, on the back of this form.

EXPLAIN, AS NECESSARY, ANY OF THE FOREGOING ITEMS ON THE BACK OF THIS FORM.

/S/ 11/6/97

Signature of Preparer and Title (PM, CSO, MO, other) Date

/S/ 11/22/97

cc: Orig NDA/PLA # 20-774
HFD-540 /Div File
NDA/PLA Action Package
HFD-510/GTroendle (plus, for CDER APs and AEs, copy of action letter and labeling)

NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action.

ped5

PERIODONTITIS IS A DISEASE OF ADULTS.

Fred Hyman, DDS MPH
Dental Officer, HFD-540

11/23/97

PERIO PRODUCTS LTD.

P.O.B 23950. Jerusalem 91237 Israel Tel: 972-2-322836, Fax: 972-2-812722

DEBARMENT CERTIFICATION

I, Stanley Fass, of Perio Products, Ltd., in my capacity as President, certify in accordance with the requirements of the Generic Drug Enforcement Act of 1992 (Pub. L. No. 102-282, 306 (k), 106 Stat. 149, 158) that Perio Products, Ltd., in connection with this NDA, has not, and will not use in any capacity, the services of any person (including a corporation, partnership, association or individual), who has been debarred from submitting or assisting in the submission of a drug application to the Food and Drug Administration by the Secretary of Health and Human Services, pursuant to Authority conferred to the Secretary, under section 306 (a), and section 306 (b), 106 Stat. 149, 150-152 (1992).

Signature: Stanley Fass

Title: President

Date: September 18, 1996

MEMO OF T-CON

NDA 20-774 Perio Chip (chlorhexidine gluconate)

DATE: August 21, 1997

TIME: 9:30 a.m.

MEETING CHAIR: Dr. James Vidra

PROJECT MANAGER: Harold Blatt

PARTICIPANTS:

FDA
James Vidra, Ph.D., Chemistry Reviewer, HFD-540
Harold Blatt, Project Manager, HFD-540

AND

Oxford Research (U.S. Agent for Perio Products)
Robert McCormack, Ph.D., Reg. Affairs

OBJECTIVE: To explain the new ruling on Environmental Assessment (EA), to offer the sponsor options on how to respond to this new ruling, and to provide an update on the status of our CMC review.

DISCUSSION: Introductions were made and the following issues was discussed:

1.The sponsor was told that the new ruling on EAs will become effective after 8-28-97. The sponsor was informed they will need to submit a formal letter stating that their product pollutes the aquatic environment at less than 1 part per billion (ppb) and that they therefore are requesting a categorical exclusion. The sponsor was also informed that they do not have to request a categorical exclusion if they wish.

The sponsor stated that they do intend to make the request and will be sending a formal letter to the FDA soon.

2. The sponsor also requested an update on the status of the CMC review. FDA stated that the review has been started. Current attention is being given to the DMFs. The sponsor was informed that will have to be deleted from the bulk drug suppliers. The sponsor informed FDA that only the material from will be used for marketing. The Division has only received unofficial notice that bulk suppliers have passed inspection.

3. The Division will send the sponsor an information request if we find anything that looks like a problem.

/S/

8-21-97

Minutes Preparer and Project Manager, HFD-540

/S/

8/21/97

Concurrence Chair, HFD-540

cc:
Orig NDA 20-774
HFD-540/DIV FILES
HFD-540/Vidra
HFD-540/Blatt

n20774.821

RECORD OF TELEPHONE CONVERSATION	DATE: May 7, 1998, 11:30 AM
I called Dr. McCormack and told him that a single sentence had been added to the Pharmacokinetics section as a result over concerns over the use of the regulatory specification method as compared to an experimental method for assessing drug release. The sentence reads, Dr. McCormack was agreeable to this change in labeling. cc: NDA 20-774 Division File HFD-540\Blay	NDA NUMBER 20-774 IND NUMBER xxxxxxxx TELECON INITIATED BY: APPLICANT/SPONSOR; (FDA) MADE: (BY TELEPHONE); IN PERSON PRODUCT NAME PerioChip FIRM NAME Target Research NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD Dr. Robert McCormack TELEPHONE 908-322-2402
SIGNATURE 5/7/98 Roy A. Blay	DIVISION HFD-540, DDDDP

RECORD OF TELEPHONE CONVERSATION	DATE: October 10, 1997, 2:50 PM
I called Dr. McCormack and asked him to supply in vitro release rate data on chlorhexidine release from the PerioChip beyond the hour data currently supplied. The labeling calls for days of release, but submitted data does not support this claim. Either additional data to cover this period of drug release should be submitted or a rationale should be supplied as to why such data is not needed. Dr. McCormack said that PK information on in vivo release is available, but he believes that in vitro data is not available. He will supply a rationale as to why in vitro data is not necessary if the in vitro data is not available. cc: NDA 20-774 Division File HFD-540\Blay\Vidra 10/10/97	NDA NUMBER 20-774 IND NUMBER xxxxxxxx TELECON INITIATED BY: APPLICANT/ SPONSOR; FDA MADE: BY TELEPHONE; IN PERSON PRODUCT NAME PerioChip FIRM NAME Target Research NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD Dr. Robert McCormack TELEPHONE 908-322-2402
SIGNATURE 10/10/97 Roy A. Blay	DIVISION HFD-540, DDDDP

Minutes of Teleconference

Date:	September 29, 1997, 9:00 AM
Sponsor:	Perio Products Ltd.
Agent:	PerioChip, NDA 20-774
Purpose:	Discussion of Biopharmaceutics Issues

FDA Attendees

John V. Kelsey, D.D.S., M.B.A., Dental Team Leader
Roy Blay, Ph.D., Project Manager RB 10/24/97
Dennis Bashaw, Pharm.D., Biopharmaceutics Team Leader
Fred Hyman, D.D.S., M.P.H., Dental Officer

Sponsor Attendees

Robert J. Mc Cormack, Ph.D., V.P. Reg. Affairs, Target Research Assoc., Inc.,
Moshe Flashner-Barak, Ph.D., Senior V.P., Technology, Perio Products, Ltd.

Dr. Hyman made initial introductory remarks on the concern that the Division had regarding the intended labeling for the use of 8 PerioChips™ rather than 4 as used in the pivotal clinical trials. Dr. Bashaw confirmed that the sponsor was proposing the use of up to 8 PerioChips™ at one time as described in their draft labeling. Dr. Bashaw noted that the sponsor had not provided any data or a rationale that would allow for a link between the use of 4 chips as studied and the use of 8 chips as proposed. Dr. McCormack confirmed that this issue was not addressed in the NDA submission.

Dr. Bashaw suggested that the sponsor submit published literature, perhaps using information on chlorhexidine oral solution, to provide information on the margin of safety that would be present if 8 chips were to be used at once.

Dr. McCormack said that they would submit an answer in writing and provide calculations that would demonstrate that any absorption would be below the level of detection and support the proposed use of 8 chips.

Dr. McCormack said that requested microbiology information was also about to be submitted for review.

Concurrences: FHyman, 9.29.97; JKelsey, 9.29.97; EDBashaw, 10.20.97

cc:
NDA 20-774
NDA Arch.
HFD-540/Blay/Hyman/Kelsey/See
HFD-880/Bashaw
HFD-520/Marsik

JAN 2 1997

NDA 20-774

Robert J. McCormack, Ph.D.
Oxford Research International Corp.
1425 Broad Street
Clifton, NJ 07013-4221

Dear Dr. McCormack:

We have received your New Drug Application (NDA) submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product:	Perio Chip (chlorhexidine gluconate) 2.5 mg
Date of Application:	December 20, 1996
Date of Receipt:	December 20, 1996
Our Reference Number:	NDA 20-774

Unless we find the application not acceptable for filing, the filing date will be February 18, 1997.

Please begin any communications concerning this application by citing the NDA number listed above. Should you have any questions concerning the NDA, please contact:

Harold Blatt
Project Manager
(301) 827-2023

Sincerely yours,

/S/ 1/2/97

Mary Jean Kozma-Fornaro
Acting Supervisor, Project Management Staff
Division of Dermatologic
and Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation & Research

cc: Orig. NDA 20-774
HFD-92
HFD-540
HFD-540/CSO/Blatt
MO/
PHARM/See
CHEM/DeCamp
TECH/Childs/12/30/96
ACKNOWLEDGMENT LETTER

BC
ORIG AMENDMENT

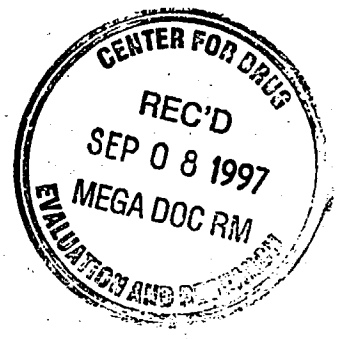
ORIGINAL

Oxford Research International Corp.

AFFILIATE OF
ORD PHARMACEUTICAL SERVICES, INC.

1425 BROAD STREET
CLIFTON, NEW JERSEY 07013-4
(201) 777-2800

September 5, 1997



Johnathan K. Wilkin, M.D.
Director
Division of Dermatological and Dental Products (HFD-540)
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation V
9201 Corporate Blvd.
Rockville, MD 20857

RE: Request for a claim for Categorical Exclusion of the Environmental Assessment for the Periochip NDA (No. 20-774)

Dear Dr. Wilkin:

On Tuesday, July 29, 1997, FDA published a Federal Register Notice which became effective on August 28, 1997 that revised the National Environmental Policy Act to include among other things, a claim for categorical exclusion of an Environmental Assessment (EA) if the concentration of the active moiety at the point of entry into the aquatic environment is below 1 part per billion (ppb). Additionally, the Federal Register Notice allows applicants to submit an amendment claiming categorical exclusion for an EA contained in an application that was pending before the Agency as of August 28, 1997 and for which the agency had not yet signed a finding of no significant impact.

The NDA (No. 20-774) for the Periochip was submitted to the Agency on December 20, 1996. In accordance with 21 CFR 25.31a(b)(3) the application contained an abbreviated Environmental Assessment Report which contained information to demonstrate that the environmental introduction concentration (EIC) of the drug product is < 1 ppb. Therefore, as per the July 29, 1997 Federal Register Notice, we are hereby requesting on behalf of Perio Products, Ltd., a claim for categorical exclusion of the EA submitted in the Periochip NDA based on the EIC of the active moiety being < 1 ppb. Enclosed is a copy of Page 081 of the Environmental Assessment Report contained in Volume 1.4 of the Periochip NDA which shows the EIC for the Periochip is projected to be < 1 ppb.

FAX: (201) 777-127
FAX: (201) 777-984

Please let me know if you have any questions.

Sincerely,

Robert J. McCormack, Ph.D.
V.P. Regulatory Affairs

RMC/bc

Enclosure

Item 6. Introducing Substance into the Environment

a. *Active Substance*:

DMF No

Facilities Environmental Operating Compliance Statement: (Item 14 Appendix)

b. *Drug Product - Manufacture:*

Attached please find the certificate issued by the Jerusalem Municipality (Item 14. Appendix).

c. *Drug Product - End Use:*

Returned, rejected or expired drug product will be disposed of in an appropriate manner according to procedures established by with subsequent incineration as non-hazardous solid waste at a licensed facility in accordance with local, State and Federal Regulations. Information on the contract facility is found in Item 4.c.ii.

Expected Introduction of Concentrations:

The expected introduction concentrations in the environment are minimal based on the following:

1. All of the waste materials generated by the Perio Chip production process are transferred for incineration or burial.

2. The only waste introduced into the central sewage system results from the washing water used to clean the reactor. This concentration has been calculated to be only g chlorhexidine gluconate per batch of kg.

3. The drug product market forecast for the fifth year of production will be approximately chips (kg per year of active ingredient). By calculation, the potential environmental introduction concentration is < 1 ppb and qualifies for a Tier 0 approach. Assuming that all drug product is used, the EIC for the aquatic environment is calculated to be:

$$70\ \text{kg/yr} \times \frac{1}{1.115 \times 10^{11}\ \text{L/day}} \times \frac{\text{yr}}{365\text{da}} \times \frac{10^{9}\ \mu\text{g}}{\text{kg}} = <1\ \text{ppb}$$

Item 12. List of Preparers

Rami Kariv M.Sc. Ph.D. Chief Pharmacist, Perio Products Ltd.
Emil Weisenberg Dr. Pharm. Ph.D., Consultant
Richard Benoit, R Ph., Manager of Corporate Safety, Astra USA
Oxford Research International Corp. (CRO) Consultant

NDA 20-774
PerioChip™, Chlorhexidine Gluconate, 2.5 mg

ADDENDUM TO THE ORIGINAL NDA 20-774 CMC REVIEW

The following chlorhexidine gluconate article appeared in the attached October 6, 1997 Federal Register/Vol.62, No.193, pages 52,137-52,138 and reviewed as an addendum to the CMC Review of this NDA. The contents of this article are summarized below:

The FDA has withdrawn the chlorhexidine gluconate topical tincture, 0.5% (Hibitane) from sale for reasons of safety. The Agency will not accept abbreviated ANDAs for this product.

Copies of this Federal Register Reference were transmitted to the Chemistry Supervisor, to the Dental Officer Team Leader and to the Pharmacological/Toxicology Reviewer on October 23, 1997.

/S/

James D. Vidra, Ph.D.
Review Chemist, HFD-830/HFD-540

Attachment

10-6-97
Vol. 62 No. 193

Federal Register

Monday
October 6, 1997

FR 10/6/97
p 52137
CHG 2.5% withdrawn
for safety

United States
Government
Printing Office
SUPERINTENDENT
OF DOCUMENTS
Washington, DC 20402

OFFICIAL BUSINESS
Penalty for private use, $300

PERIODICALS
Postage and Fees Paid
U.S. Government Printing Office
(ISSN 0097-6326)

0 C St. SW., Washington, DC 20204, 2–418–3086.

SUPPLEMENTARY INFORMATION: Under the Federal Food, Drug, and Cosmetic Act (sec. 409(b)(5) (21 U.S.C. 348(b)(5))), notice is given that a food additive petition (FAP 7B4549) has been filed by Mitsui Petrochemical Industries, Ltd., c/o Keller and Heckman LLP, 1001 G St. NW., suite 500 West, Washington, DC 20001. The petition proposes to amend the food additive regulations in § 177.1520 *Olefin polymers* (21 CFR 177.1520) to provide for the safe use of ethylene/propylene copolymers that contain up to 20 mole-percent of polymer units derived from propylene, with the remainder of the polymer consisting of ethylene, and having a minimum viscosity-average molecular weight of 95,000 and a minimum Mooney viscosity of 13 at up to 30 percent of other regulated polymer blends.

The potential environmental impact of this action is being reviewed. To encourage public participation consistent with regulations promulgated under the National Environmental Policy Act (40 CFR 1501.4(b)), the agency is placing the environmental ɔssment submitted with the petition is the subject of this notice on ɔlic display at the Dockets Management Branch (address above) for public review and comment. Interested persons may, on or before November 5, 1997 submit to the Dockets Management Branch (address above) written comments. Two copies of any comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. Received comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday. FDA will also place on public display any amendments to, or comments on, the petitioner's environmental assessment without further announcement in the Federal Register. If, based on its review, the agency finds that an environmental impact statement is not required and this petition results in a regulation, the notice of availability of the agency's finding of no significant impact and the evidence supporting that finding will be published with the regulation in the Federal Register in accordance with 21 CFR 25.40(c).

Dated: September 17, 1997.

M. Rulis

or, Office of Premarket Approval, ..er for Food Safety and Applied Nutrition.

[FR Doc. 97–26452 Filed 10–3–97; 8:45 am]

BILLING CODE 4160–01–F

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 97F–0414]

Stilbene Whitening Agent Task Force; Filing of Food Additive Petition

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is announcing that the Stilbene Whitening Agent Task Force has filed a petition proposing that the food additive regulations be amended to provide for the safe use of benzenesulfonic acid,2'2'-(1,2-ethenediyl)bis[5-[[4-[bis(2-hydroxyethyl-amino]-6-[(4-sulfophenyl)amino]-1,3,5-triazin-2-yl]amino]-,tetrasodium salt as an optical brightener in paper and paperboard intended for use in contact with food.

FOR FURTHER INFORMATION CONTACT: Hortense S. Macon, Center for Food Safety and Applied Nutrition (HFS–205), Food and Drug Administration, 200 C St. SW., Washington, DC 20204, 202–418–3086.

SUPPLEMENTARY INFORMATION: Under the Federal Food, Drug, and Cosmetic Act (sec. 409(b)(5) (21 U.S.C. 348(b)(5))), notice is given that a food additive petition (FAP 7B4554) has been filed by Stilbene Whitening Agent Task Force, c/o Keller and Heckman LLP, 1001 G St. NW., suite 500 West, Washington, DC 20001. The petition proposes to amend the food additive regulations in § 176.170 *Components of paper and paperboard in contact with aqueous and fatty foods* (21 CFR 176.170) to provide for the safe use of benzenesulfonic acid,2'2'-(1,2-ethenediyl)bis[5-[[4-[bis(2-hydroxyethyl)-amino]-6-[(4-sulfophenyl)amino]-1,3,5-triazin-2-yl]amino]-, tetrasodium salt as an optical brightener in paper and paperboard intended for use in contact with food.

The agency has determined under 21 CFR 25.32(i) that this action is of the type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

Dated: September 17, 1997.

Alan M. Rulis,

Director, Office of Premarket Approval, Center for Food Safety and Applied Nutrition.

[FR Doc. 97–26453 Filed 10–3–97; 8:45 am]

BILLING CODE 4160–01–F

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 96P–0181]

Determination that Chlorhexidine Gluconate Topical Tincture 0.5% Was Withdrawn From Sale for Reasons of Safety

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) has determined that chlorhexidine gluconate topical tincture 0.5% (Hibitane®) was withdrawn from sale for reasons of safety. The agency will not accept abbreviated new drug applications (ANDA's) for chlorhexidine gluconate topical tincture 0.5%.

FOR FURTHER INFORMATION CONTACT: Christine F. Rogers, Center for Drug Evaluation and Research (HFD–7), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–594–2041.

SUPPLEMENTARY INFORMATION: In 1984, Congress passed into law the Drug Price Competition and Patent Term Restoration Act of 1984 (Pub. L. 98–417) (the 1984 amendments), which authorized the approval of duplicate versions of drug products approved under an ANDA procedure. ANDA sponsors must, with certain exceptions, show that the drug for which they are seeking approval contains the same active ingredient in the same strength and dosage form as the listed drug, which is a version of the drug that was previously approved under a new drug application (NDA). Sponsors of ANDA's do not have to repeat the extensive clinical testing otherwise necessary to gain approval of an NDA. The only clinical data required in an ANDA are data to show that the drug that is the subject of the ANDA is bioequivalent to the listed drug.

The 1984 amendments included what is now section 505(j)(6) of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 355(j)(6)), which requires FDA to publish a list of all approved drugs. FDA publishes this list as part of the "Approved Drug Products with Therapeutic Equivalence Evaluations," which is generally known as the "Orange Book." Under FDA regulations, drugs are withdrawn from the list if the agency withdraws or suspends approval of the drug's NDA or ANDA for reasons of safety or effectiveness, or if FDA determines that the listed drug was

hdrawn from sale for reasons of ety or effectiveness (§ 314.162 (21 CFR 314.162)).

FDA regulations provide that any person may petition the agency for a determination as to whether a listed drug has been voluntarily withdrawn from sale for reasons of safety effectiveness (§ 314.161(b) (21 CFR 314.161(b))). Richard A. Hamer submitted a citizen petition dated May 24, 1996, under 21 CFR 10.25(a), 10.30, and 314.122(a), requesting that the agency determine whether chlorhexidine gluconate topical tincture 0.5% (Hibitane®) was withdrawn from sale for reasons of safety or effectiveness. Zeneca Pharmaceuticals (formerly Steuart Pharmaceuticals and ICI Americas) obtained approval of NDA 18–049 for chlorhexidine gluconate topical tincture 0.5% on December 18, 1978, as a patient preoperative skin preparation. The product was withdrawn from sale by the sponsor in early 1984. Because the sponsor discontinued marketing of the product, the agency currently lists chlorhexidine gluconate topical tincture 0.5% in the Orange Book's "Discontinued Drug oduct List."

FDA has reviewed its records and, under §§ 314.161 and 314.162(a)(2), has determined that chlorhexidine gluconate topical tincture 0.5% was withdrawn from sale for reasons of safety. Specifically, the product was withdrawn because of the significant number of reports received concerning chemical and thermal burns associated with the use of the product. Therefore, chlorhexidine gluconate topical tincture 0.5% will be removed from the list of drug products with effective approvals published in FDA's publication, "Approved Drug Products with Therapeutic Equivalence Evaluations." FDA will not accept ANDA's that refer to this drug product.

Dated: September 26, 1997.

William K. Hubbard,

Associate Commissioner for Policy Coordination.

[FR Doc. 97–26353 Filed 10–3–97; 8:45 am]

BILLING CODE 4160–01–F

500 mgs/100 mls

of Tincture
0.5% = 0.5 gms / 100 gms/mls. = 5 mgs/ml
= 5 mgs/gm

Iodex = 0.12% = 1.2 mgs/ml

10 Chip = 2.5 mgs (of 20% Soln.) = 0.5 mgs / 7.5 mg chip
7.5 mg chip

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 97D–0410]

Guidance for Industry on SUPAC–MR, Modified Release Solid Oral Dosage Forms; Scale-Up and Postapproval Changes for Chemistry, Manufacturing, and Controls; Availability

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is announcing the availability of a guidance for industry entitled "SUPAC–MR: Modified Release Solid Oral Dosage Forms; Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls; In Vitro Dissolution Testing and In Vivo Bioequivalence Documentation." The purpose of this guidance document is to provide insight and recommendations to pharmaceutical sponsors of new drug applications (NDA's), abbreviated new drug applications (ANDA's), and abbreviated antibiotic applications (AADA's) who intend to change the components or composition, the manufacturing (process or equipment), the scale-up/scale-down of manufacture, and/or the site of manufacture of a modified release solid oral formulation during the postapproval period. This guidance document represents the agency's current thinking on scale-up and postapproval changes (SUPAC) for modified release solid oral dosage forms regulated by the Center for Drug Evaluation and Research (CDER).

DATES: Written comments may be submitted at any time.

ADDRESSES: Submit written requests for single copies of "SUPAC–MR: Modified Release Solid Oral Dosage Forms; Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls; In Vitro Dissolution Testing and In Vivo Bioequivalence Documentation" to the Drug Information Branch (HFD–210), Center for Drug Evaluation and Research, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857. Send two self-addressed adhesive labels to assist that office in processing your requests. Submit written comments on the guidance document to the Dockets Management Branch (HFA–305), Food and Drug Administration, 12420 Parklawn Dr., rm. 1–23, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT: Mehul U. Mehta, Center for Drug Evaluation and Research (HFD–860), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–594–0501.

SUPPLEMENTARY INFORMATION: FDA is announcing the availability of a guidance for industry entitled "SUPAC–MR: Modified Release Solid Oral Dosage Forms; Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls; In Vitro Dissolution Testing and In Vivo Bioequivalence Documentation." The purpose of this guidance document is to provide insight and recommendations to pharmaceutical sponsors of NDA's, ANDA's, and AADA's who intend to change: (1) The components or composition; (2) the manufacturing (process or equipment); (3) the scale-up/scale-down of manufacture; and/or (4) the site of manufacture of a modified release solid oral formulation during the postapproval period. The guidance document defines the following: (1) Levels of change; (2) recommended chemistry, manufacturing, and controls (CMC) tests to support each level of change; (3) recommended in vitro dissolution release tests and/or in vivo bioequivalence tests to support each level of change; and (4) documentation to support the change.

For postapproval changes for modified release dosage forms that affect components and composition, manufacturing process or equipment changes, scale-up, and site change, this guidance supersedes the recommendations in section 4.G of the *Office of Generic Drugs Policy and Procedure Guide 22–90* (FDA, September 11, 1990). For all other dosage forms and changes, this guidance does not affect the recommendations in *Guide 22–90.*

This guidance document represents the agency's current thinking on SUPAC for modified release solid oral dosage forms regulated by CDER. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both.

Interested persons may, at any time, submit written comments on the guidance document to the Dockets Management Branch (address above). Two copies of any comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. A copy of the guidance

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-774

CORRESPONDENCE

TARGET RESEARCH ASSOCIATES
CLINICAL RESEARCH, REGULATORY AFFAIRS & BIOSTATISTICS

ORIG AMENDMENT

ORIGINAL

April 28, 1998

Jonathan K Wilkin, M.D.
Director
Office of Drug Evaluation V (HFD-540)
Division of Dermatological and Dental Drug Products
Center for Drug Evaluation and Research
5600 Fishers Lane
Rockville, MD 20875

RE: PerioChip™ NDA #20-774
Eighteen (18) Month Stability Update

Dear Dr. Wilkin:

Reference is made to the PerioChip NDA (#20-744) which was initially submitted to the Agency on December 20, 1996 and the subsequent amendment submitted on September 18, 1997 containing the one-year stability update.

During the June 17, 1996 pre-NDA meeting with the Agency it was agreed that updated stability data would be submitted periodically. Therefore, we are hereby submitting, in duplicate, and on behalf of Perio Products, Ltd., updated stability tables showing up to eighteen (18) month, real time results for the three primary stability lots (R-369, R-370, R-371). The enclosed tables update those submitted in Vol. 1.4, Pages 044-061 in the original NDA. Please note that there has been a recalculation of the p-Chloroaniline (PCA) content data results. The values were changed to reflect the revised analytical method Issue:9 US to determine the PCA content in the PerioChip™ which was submitted as a NDA amendment on December 20, 1997. A recalculation of the PCA data results was performed to the real-time (5°C) and the completed accelerated (10°C and 20°C) stability studies.

The acceptable stability results accumulated from the primary and supportive studies indicate a proposed shelf life of 24 months under refrigerated (2-8°C) storage conditions may be established. In accordance with 21CFR314.70(d)(5) and as provided in the NDA stability protocol submitted in Vol. 1.4/pg. 042 in the application, the sponsor intends to

further extend the expiration date post-approval, based upon full shelf-life acceptable stability data.

If there should be any questions or need for clarifications, please contact me.

Sincerely,

Robert J. McCormack, Ph.D.
Vice President, Regulatory Affairs

RJM:jt
Enclosure(s)

NC
NEW CORRESP
ORIGINAL

TARGET RESEARCH ASSOCIATES
CLINICAL RESEARCH, REGULATORY AFFAIRS & BIOSTATISTICS

April 17, 1998

Dr. Roy Blay
Project Manager
Division of Dermatologic and Dental Drug Products
HFD-540
Food and Drug Administration
Office for Drug Evaluation and Research
Office of Drug Evaluation V
9201 Corporate Blvd.
Rockville, MD 20850

RE: Perio Products LTD.
PerioChip NDA #20-774
Acceptance of Labeling

Dear Dr. Blay:

This letter will serve as formal notification that Perio Products has accepted without condition the labeling for the PerioChip which was sent to me on April 16, 1998.

We look forward to receiving the NDA approval letter in the near future.

Thank you for all your help and assistance related to the PerioChip NDA.

Sincerely,

Robert J. McCormack, Ph.D.
Vice President, Regulatory Affairs

RJM:jt

TARGET RESEARCH ASSOCIATES

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CAL RESEARCH, REGULATORY AFFAIRS & BIOSTATISTICS

ORIGINAL

3/30/98 Noted. There is no clinical information in this submission

Fred Hyman

March 12, 1998

Jonathan K. Wilkin, M.D.
Office of Drug Evaluation V (HFD-540)
Division of Dermatological and Dental Drug Products
Center for Drug Evaluation and Research
5600 Fishers Lane
Rockville, MD 20875

Re: PerioChip NDA #20-774
Response to NDA Non Approvability Issues Outlined in FDA Correspondence Dated November 25, 1997

Dear Dr. Wilkin:

Reference is made to the PerioChip NDA (#20-774) received at the Agency on December 20, 1996, and to FDA correspondence dated November 25, 1997 which states that the NDA is approvable. In the November 25, 1997 letter several non-approvable issues were requested to be addressed. The purpose of this submission therefore, is to provide in duplicate, on behalf of Perio Products, a response to each of the non-approvable issues outlined in the November 25, 1997 letter.

We trust that the information provided adequately addresses each of the non-approvable issues. Perio Products will provide a more detailed response related to the in- vitro release rate specification issue once more data becomes available.

Please let me know if you have any questions.

Sincerely,

RJMcormack for

Robert J. McCormack, Ph.D.
Vice-President, Regulatory Affairs

RJM:jt

NC
20-774

ORIGINAL

NEW CORRESP

January 13, 1998

MEDWATCH
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20852-9787

Re: Perio Chip End of Year Report-Summary of Serious Adverse Events Reported to FDA, 1997

Dear Sir or Madam:

Attached please find a report summary of all Serious Adverse Events Reported for the PerioChip during 1997.

Sincerely,

Brenda Kolatch